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EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,299	HAGER, JOERG	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-30,32,34,36,39 and 54-56* is/are pending in the application.

4a) Of the above claim(s) *46-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-30,32,34,36,39 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/12/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. This action is in response to Applicant's response, filed on April 27, 2004. Currently, Claims 23-30, 32, 34, 36, 39, and 46-56 are pending. Claims 23-30, 32, 34, 36, 39, and 54-56 are rejected herein, and Claims 46-53 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821. This action contains new rejections necessitated by Applicant's amendments. Accordingly, this action is made FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

MAINTAINED REJECTION

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite over "chromosome-specific and sequence-specific fashion" because it is not clear as to what steps encompass cloning in a "chromosome-specific and sequence-specific *fashion*", and furthermore, this methodology is not defined in the specification. It is not clear whether this refers to the use of specific vectors or whether there is a specific process by which to clone in a "chromosome-specific and sequence-specific fashion".

Applicants Arguments

Applicant argues the recitation of "chromosome-specific and sequence-specific fashion" is defined in the specification, and that the use of any particular vector is not required. Furthermore, Applicant argues page 13, lines 17-27 indicate a specific process by which to clone in a "chromosome-specific and sequence-specific fashion," namely, homologous recombination.

Response to Applicants Arguments

Applicant's arguments have been considered, but are not persuasive for the following reasons. First, the recitation of "chromosome-specific and sequence-specific fashion" is not specifically defined in the specification, nor is this recitation an art-recognized phrase. Page 13, lines 20-21, recites, "the restriction fragments may be cloned in a chromosome-specific and sequence-specific fashion." The specification continues by giving a single example of a "chromosome-specific and sequence-specific fashion," namely, homologous recombination. However, providing an example of a process by which a restriction fragment can be cloned into a vector is not equivalent to providing a completely clear definition. Accordingly, because "chromosome-specific and sequence-specific fashion" is not an art-recognized term, and because there is not a clear definition of this recitation in the specification, the rejection is maintained.

NEW REJECTIONS NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 23-29, 32, 34, 36, 39, and 54-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (USPN 6,287,825).

Regading Claim 1, Weissman teaches a method comprising:

(a) digesting separately nucleic acids from a mixture of at least two nucleic acid populations with at least one restriction enzyme (see col. 4, lines 45-48, col. 7, lines 45-46, and cols. 11-14, for example);

(b) ligating an adaptor sequence to the restriction fragments (see col. 4, line 57 to col. 5, line 3, and col. 7, lines 50-53, and cols. 11-14, for example);

(c) amplifying adaptor-ligated restriction fragments generated in step (b) and in step (b) using an adaptor-specific primer to produce amplification products having different ends in respect to each of the at least tow nucleic acid populations (see col. 2, 54-59, col. 4, line 57 to col. 5, line 3, and cols. 11-14, for example);

(d) hybridizing the amplification products of step (c) from the different nucleic acid populations with each other to generate a mixture comprising homoduplexes and heteroduplexes (see col. 5, line 57 to col. 6, line 1, and cols. 11-14, for example); and

(f) eliminating mismatched heteroduplexes by using mismatch repair enzymes (see cols. 1-3 and 6-7, for example); and

(g) identifying, isolating, or separating fully-matched heteroduplexes, thereby identifying, isolating or separating nucleic acid fragments that are identical between the at least two nucleic acid populations (see col. 6, lines 2-8, col. 3, and cols. 11-14, for example).

Furthermore, Weissman teaches:

> The methods employed in this invention depend on the isolation of heterohybrid DNA in which the two strands are derived from two different DNA samples. This can be accomplished by published methods (Nelson, et al., cited above). Improved procedures that do not require methylation of fragment DNA are included in this invention. Sequences in the adapters are designed to allow selective cutting of homohybrid or heterohybrid DNA with restriction endonucleases. In some methods, the adapters contain two adjacent restriction enzyme recognition sites with specific methylation patterns such that heterohybrid and homohybrid DNAs can be distinguished by the ability of the methyl groups to block cutting by the restriction endonuclease. In other methods, partial restriction endonuclease recognition sequences are present in which the adapter contains mismatched bases. In this case heterohybrid and homohybrid DNAs can be distinguished by the elimination of the mismatches which allows restriction endonuclease to cut these sites.

(See col. 7, lines 3-22). Therefore, Weissman teaches that homoduplexes and heteroduplex can be distinguished and eliminated by using enzymes. (See also col. 1 and 3) Weissman further suggests eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments (see col. 1, teaching the digestion of Exo III eliminates homoduplexes from heteroduplexes) (step (e) of the claimed invention).

Accordingly, while Weissman does not specifically exemplify eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments (e.g., Exo III), he suggests using an enzyme that specifically digests blunt-ended double-stranded DNA fragments (e.g., Exo III) for eliminating blunt ended homoduplexes from heteroduplexes having forked ends. Therefore, in view of the teachings of Weissman, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used an enzyme that specifically digests blunt-ended double-stranded DNA fragments (e.g., Exo III), in order to have achieved the benefit of eliminating blunt ended homoduplexes from heteroduplexes having forked ends for use genetic analysis.

Regarding Claims 24-25, Weissman teaches the nucleic acid populations comprise human genomic DNA populations (see col. 4, lines 52-56, for example).

Regarding Claims 26-28, Weissman teaches the nucleic acid populations comprise nucleic acid populations from different subjects (or sources) having a common trait of interest and selected chromosomes (e.g., human chromosomes) (see abstract and cols. 1, 3 and 4, for example).

Regarding Claim 29, Weissman teaches the restriction fragments are size-selected prior to amplification (see cols. 4-5 and 7, for example). It is noted that Weissman's teaching of ligating adaptors only to restriction fragments can be interpreted as only amplifying "size-selected" fragments, as sequences that do not have adaptors are not selected for amplification.

Regarding Claims 32, Weissman teaches the adaptors (Y-shaped, dsDNA adaptors comprising at least a 5 base long fragment) can contain restriction endonuclease sites for elimination of homohybrids or heterohybrids, such a recognition site can be GATC, which is specific for mutHL (see cols. 1, 3, 7-8 and Figure 1(a), for example).

Regarding Claim 34, Weissman teaches the amplification can be via PCR (see col. 2, lines 54-59, and col. 5, lines 4-22, for example).

Regarding Claim 36, Weissman teaches the primer can be labeled with a biotin tag at its 5' end (see col. 3, lines 7-11, col. 5, lines 24-35, for example).

Regarding Claims 39, Weissman teaches the eliminating step occurs via mismatch repair enzymes, such as MutH, MutS and MutL (see cols. 1-2, for example).

Regarding Claims 54-56, Weissman teaches using Exo III, and further eliminating newly created single strands by binding said newly created single strands to a single strand-specific matrix (see col. 1, for example).

Applicants Arguments

Applicant argues Weissman does not teach step (e), eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments. Applicant also argues Weissman does not teach eliminating mismatched heterohybrids after specific elimination

of blunt-ended homoduplexes. Applicant further argues Weissman does not teach cloning prior to amplification.

Response to Applicants Arguments

Applicant's arguments have been considered, but are not persuasive for the following reasons. First, as stated above, Weissman suggests performing step (e) of the newly amended claim. Next, the claims do not specifically require eliminating mismatched heterohybrids *after* specific elimination of blunt-ended homoduplexes. Furthermore, the order of performing step (e) or (f) is not critical, since the end goal is to obtain mismatched heterohybrids. Therefore, even assuming Weissman did not teach eliminating mismatched heterohybrids *after* specific elimination of blunt-ended homoduplexes (which he does at col. 1), the switching of the order of steps (e) and (f) is not inventive. Applicant's argument that Weissman does not teach cloning prior to amplification has been found persuasive.

8. Claims 23-29 and 34-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Weissman et al. (USPN 6,150,112).

Regarding Claim 1, Weissman teaches a method comprising:

(a) digesting separately nucleic acids from a mixture of at least two nucleic acid populations with at least one restriction enzyme (see col. 2, lines 46-48, col. 4, lines 30-34, and col. 6, lines 33-36, for example);

(b) ligating an adaptor sequence to the restriction fragments (see col. 4, line 40 to col. 5, line 5, and col. 6, lines 37-38, for example);

(c) amplifying adaptor-ligated restriction fragments generated in step (b) and in

step (b) using an adaptor-specific primer to produce amplification products having different ends in respect to each of the at least tow nucleic acid populations (see col. 4, line 40 to col. 5, line 5, and col. 6, lines 39-48, for example);

(d) hybridizing the amplification products of step (c) from the different nucleic acid populations with each other to generate a mixture comprising homoduplexes and heteroduplexes (see col. 5, lines 15-23, Figure 1(f), and col. 6, lines 57-65, for example); and

(f) eliminating mismatched heteroduplexes by using mismatch repair enzymes (see cols. 1-3 and 5-7, for example)

(g) identifying, isolating, or separating fully-matched heteroduplexes, thereby identifying, isolating or separating nucleic acid fragments that are identical between the at least two nucleic acid populations (col. 5, lines 23-28, col. 6, lines 5-9 and line 55 to col. 7, line 18, for example).

Weissman also teaches the selection of heterohybrids can be performed using the methods described by Nelson, which are described in column 1. In column 1, Weissman teaches that homoduplexes and heteroduplex can be distinguished and eliminated by using enzymes. Weissman further suggests eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments (see col. 1, teaching the digestion of Exo III eliminates homoduplexes from heteroduplexes) (step (e) of the claimed invention).

Accordingly, while Weissman does not specifically exemplify eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments (e.g., Exo III), he suggests using an enzyme that specifically digests blunt-ended double-stranded DNA fragments

(e.g., Exo III) for eliminating blunt ended homoduplexes from heteroduplexes having forked ends. Therefore, in view of the teachings of Weissman, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used an enzyme that specifically digests blunt-ended double-stranded DNA fragments (e.g., Exo III), in order to have achieved the benefit of eliminating blunt ended homoduplexes from heteroduplexes having forked ends for use genetic analysis.

Regarding Claims 24-25, Weissman teaches the nucleic acid populations comprise human genomic DNA populations (col. 2, lines 30-33, for example).

Regarding Claims 26-28, Weissman teaches the nucleic acid populations comprise nucleic acid populations from different subjects (or sources) having a common trait of interest and selected chromosomes (e.g., human chromosomes) (abstract, col. 1, col. 3, lines 32-36 and col. 4, lines 36-40, for example).

Regarding Claim 29, Weissman teaches the restriction fragments are size-selected prior to amplification (col. 2, lines 45-58, for example). It is noted that Weissman's teaching of ligating adaptors only to restriction fragments can be interpreted as only amplifying "size-selected" fragments, as sequences that do not have adaptors are not selected for amplification.

Regarding Claim 30, Weissman teaches the adaptor sequence comprises a 5 base to 100 base long ds DNA fragment (see cols. 2-5).

Regarding Claim 34, Weissman teaches the amplification can be via PCR (col. 4, lines 54-56, for example).

Regarding Claim 35, Weissman teaches the primer is complementary to at least a part of the adaptor sequence (col. 2, lines 50-55, for example).

Regarding Claim 36, Weissman teaches the primer is labeled with a biotin tag at its 5' end (col. 2, lines 55-56, for example).

Regarding Claims 39, Weissman teaches the eliminating step occurs via mismatch repair enzymes, such as MutH, MutS and MutL (cols. 1-2, for example).

Regarding Claims 54-56, Weissman teaches using Exo III, and further eliminating newly created single strands by binding said newly created single strands to a single strand-specific matrix (see col. 1, for example).

9. Claims 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (USPN 6,287,825, herein referred to as '825), as applied to Claims 23-29, 32, 34, 36, 39, and 54-56 above, and in further view of Green et al. (PNAS (1990) 87: 1213-1217).

The teachings of Weissman '825 are presented above. Weissman does not specifically exemplify cloning prior to amplification.

However, cloning restriction fragments is well known in the art. For example, Green teaches cloning prior to amplification "has proven highly efficient, allowing identification and isolation of numerous YAC clones containing specific human genes." See abstract and page 1216.

Accordingly, in view of the teachings of Green, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Weissman '825 so as to have cloned the restriction fragments (e.g., in a vector in a chromosome-specific and sequence specific fashion) prior to amplification, in order to have achieved the benefit taught of a highly efficient method of enriching and selecting a desired gene sequences (responsible for a selected trait, for example).

10. Claims 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (USPN 6,150,112, herein referred to as '112), as applied to Claims 23-29, 32, 34, 36, 39, and 54-56 above, and in further view of Green et al. (PNAS (1990) 87: 1213-1217).

The teachings of Weissman '112 are presented above. Weissman does not specifically exemplify cloning prior to amplification.

However, cloning restriction fragments is well known in the art. For example, Green teaches cloning prior to amplification "has proven highly efficient, allowing identification and isolation of numerous YAC clones containing specific human genes." See abstract and page 1216.

Accordingly, in view of the teachings of Green, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Weissman '112 so as to have cloned the restriction fragments (e.g., in a vector in a chromosome-specific and sequence specific fashion) prior to amplification, in order to have achieved the benefit taught of a highly efficient method of enriching and selecting a desired gene sequences (responsible for a selected trait, for example).

Conclusion

11. No Claims are allowable.
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
13. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Alexander H. Spiegler
August 25, 2004

CARLA J. MYERS
PRIMARY EXAMINER